



## 3-M syndrome

3-M syndrome is a disorder that causes short stature (dwarfism), unusual facial features, and skeletal abnormalities. The name of this condition comes from the initials of three researchers who first identified it: Miller, McKusick, and Malvaux.

Individuals with 3-M syndrome grow extremely slowly before birth, and this slow growth continues throughout childhood and adolescence. They have low birth weight and length and remain much smaller than others in their family, growing to an adult height of approximately 120 centimeters to 130 centimeters (4 feet to 4 feet 6 inches). Affected individuals have a normally sized head that looks disproportionately large in comparison with their body. The head may be unusually long and narrow in shape (dolichocephalic).

In addition to short stature, people with 3-M syndrome have a triangle-shaped face with a broad, prominent forehead (frontal bossing) and a pointed chin; the middle of the face is less prominent (hypoplastic midface). They may have large ears, full eyebrows, an upturned nose with a fleshy tip, a long area between the nose and mouth (philtrum), a prominent mouth, and full lips.

Affected individuals may have a short, broad neck and chest with prominent shoulder blades and square shoulders. They may have abnormal spinal curvature such as a rounded upper back that also curves to the side (kyphoscoliosis) or exaggerated curvature of the lower back (hyperlordosis). People with 3-M syndrome may also have unusual curving of the fingers (clinodactyly), short fifth (pinky) fingers, prominent heels, and loose joints. Other skeletal abnormalities, such as unusually slender long bones in the arms and legs, tall, narrow spinal bones (vertebrae), or slightly delayed bone age may be apparent in x-ray images.

3-M syndrome can also affect other body systems. Males with 3-M syndrome may produce reduced amounts of sex hormones (hypogonadism) and occasionally have the urethra opening on the underside of the penis (hypospadias). People with this condition may be at increased risk of developing bulges in blood vessel walls (aneurysms) in the brain. Intelligence is unaffected by 3-M syndrome, and life expectancy is generally normal.

A variant of 3-M syndrome called Yakut short stature syndrome has been identified in an isolated population in Siberia. In addition to having most of the physical features characteristic of 3-M syndrome, people with this form of the disorder are often born with respiratory problems that can be life-threatening in infancy.

## Frequency

3-M syndrome is a rare disorder. About 50 individuals with this disorder have been identified worldwide.

## Genetic Changes

Mutations in the *CUL7* gene cause 3-M syndrome. The *CUL7* gene provides instructions for making a protein called cullin-7. This protein plays a role in the cell machinery that breaks down (degrades) unwanted proteins, called the ubiquitin-proteasome system.

Cullin-7 helps to assemble a complex known as an E3 ubiquitin ligase. This complex tags damaged and excess proteins with molecules called ubiquitin. Ubiquitin serves as a signal to specialized cell structures known as proteasomes, which attach (bind) to the tagged proteins and degrade them. The ubiquitin-proteasome system acts as the cell's quality control system by disposing of damaged, misshapen, and excess proteins. This system also regulates the level of proteins involved in several critical cell activities such as the timing of cell division and growth.

Mutations in the *CUL7* gene that cause 3-M syndrome disrupt the ability of the cullin-7 protein to bring together the components of the E3 ubiquitin ligase complex, interfering with the process of tagging other proteins with ubiquitin (ubiquitination). It is not known how impaired ubiquitination results in the specific signs and symptoms of 3-M syndrome.

## Inheritance Pattern

This condition is inherited in an autosomal recessive pattern, which means both copies of the gene in each cell have mutations. The parents of an individual with an autosomal recessive condition each carry one copy of the mutated gene, but they typically do not show signs and symptoms of the condition.

## Other Names for This Condition

- 3-MSBN
- dolichospondylic dysplasia
- Le Merrer syndrome
- three-M slender-boned nanism
- three M syndrome
- Yakut short stature syndrome

## **Diagnosis & Management**

### Genetic Testing

- Genetic Testing Registry: Three M syndrome 1  
<https://www.ncbi.nlm.nih.gov/gtr/conditions/C1848862/>

### Other Diagnosis and Management Resources

- GeneReview: 3-M Syndrome  
<https://www.ncbi.nlm.nih.gov/books/NBK1481>

### General Information from MedlinePlus

- Diagnostic Tests  
<https://medlineplus.gov/diagnostictests.html>
- Drug Therapy  
<https://medlineplus.gov/drugtherapy.html>
- Genetic Counseling  
<https://medlineplus.gov/geneticcounseling.html>
- Palliative Care  
<https://medlineplus.gov/palliativecare.html>
- Surgery and Rehabilitation  
<https://medlineplus.gov/surgeryandrehabilitation.html>

## **Additional Information & Resources**

### MedlinePlus

- Health Topic: Dwarfism  
<https://medlineplus.gov/dwarfism.html>

### Genetic and Rare Diseases Information Center

- 3M syndrome  
<https://rarediseases.info.nih.gov/diseases/5667/3m-syndrome>

### Educational Resources

- Disease InfoSearch: Three M syndrome  
<http://www.diseaseinfosearch.org/Three+M+syndrome/7072>
- MalaCards: 3-m syndrome, cul7-related  
[http://www.malacards.org/card/3\\_m\\_syndrome\\_cul7\\_related](http://www.malacards.org/card/3_m_syndrome_cul7_related)
- Orphanet: 3M syndrome  
[http://www.orpha.net/consor/cgi-bin/OC\\_Exp.php?Lng=EN&Expert=2616](http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=2616)

## Patient Support and Advocacy Resources

- Children's Craniofacial Association  
<http://www.ccakids.com/>
- Little People of America  
<http://www.lpaonline.org/>
- MAGIC Foundation for Children's Growth  
<https://www.magicfoundation.org/>
- National Organization for Rare Disorders (NORD)  
<https://rarediseases.org/rare-diseases/three-m-syndrome/>

## GeneReviews

- 3-M Syndrome  
<https://www.ncbi.nlm.nih.gov/books/NBK1481>

## Scientific Articles on PubMed

- PubMed  
<https://www.ncbi.nlm.nih.gov/pubmed?term=%28%283-m+syndrome%5BTIAB%5D%29+OR+%28dolichospondylic+dysplasia%5BTIAB%5D%29%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+3600+days%22%5Bdp%5D>

## OMIM

- THREE M SYNDROME 1  
<http://omim.org/entry/273750>

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